Postoperative Adjuvant Treatment Options in Resected Non–Small-Cell Lung Cancer

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Abstract

Lung cancer remains the most common malignancies and the leading cause of mortality worldwide, more than 80% of which are Non–Small-Cell Lung Cancer (NSCLC). For approximately one-third of diagnosed NSCLCs with stage I–IIIA disease, surgical resection is recommended as a preferred curative treatment. Nevertheless, many resected NSCLC patients experience recurrence.

The adjuvant treatment option of patients with resected Non–Small-Cell Lung Cancer (NSCLC) remains unstandardized. At present, there are many postoperative adjuvant therapy options for resected NSCLC, including chemotherapy, targeted therapy, chemotherapy and immunotherapy. However, which adjuvant therapy is better for which patients is remaining to be explored.

With further development of ctDNA-based molecular residual disease (MRD) research, more accurate clinical trials may be needed in the future to refine more comparison of biomarker for more precise treatment in postoperative adjuvant therapy in the future.

In our manuscript, we discussed the status of possible markers and possible future clinical trials in combination with MRD. Finer patient stratification and adjuvant treatment options need to be further explored.

Full Text

The adjuvant treatment option of patients with resected Non–Small-Cell Lung Cancer (NSCLC) remains unstandardized. Over the years, adjuvant chemotherapy (ACT) after surgery is recommended for resected early-stage (IB–IIIA) NSCLC patients, regardless of *EGFR* mutation status. However, this therapy is associated with modest benefits with only 5% decrease in the risk of death for 5-year survival [1]. Therefore, adjuvant targeted therapy and adjuvant immunotherapy have been tried and expected.

In advanced NSCLC with driven gene positive, targeted therapy has become the standard regimen. ICAN study showed that *EGFR* mutation rates in stage IA-IIIA NSCLC patients were similarly to advanced NSCLC patients. In this real-word cohort of resected patients with stages I to III LUAD, regardless of postoperative stage and *EGFR* mutation status, adjuvant chemotherapy did not improve survival [2]. In resectable NSCLC with *EGFR*-mutant, targeted adjuvant therapy has been attempted and ADJUVANT (CTONG1104), EVAN (Phase 2) and RADIANT studies have shown the improvement in DFS [3, 4, 5]. However, the ability of adjuvant EGFR TKI to control the frequency of central nervous system (CNS) metastasis had not been shown to be superior to that of adjuvant ACT in CTONG1104 Trial [6]. 2020 ASCO reported the OS of CTONG1104 study, and the benefits of disease-free survival (DFS) did not translate into the benefits of OS [7]. The ADAURA study is the first global large sample phase 3 clinical study of the third generation EGFR-TKI versus placebo adjuvant therapy in patients with stage IB to IIIA EGFR-positive NSCLC, and patients in osimertinib group had significantly longer DFS than those in the placebo group. In addition, osimertinib was superior to placebo group in CNS-free DFS [8]. The final OS data is not yet available.

Similarly, immunotherapy has improved survival in advanced stage NSCLC patients with *EGFR/ALK* negative, and many trials are underway in resected NSCLC patients, including neoadjuvant and adjuvant therapy. Recently, IMpower 010 clinical results were published. IMpower 010 was the first randomised phase 3 study, which showed significant improvement in DFS with adjuvant immunotherapy following adjuvant chemotherapy in patients with resected stage IB–IIIA NSCLC [9]. Based on the results of PhaseIII IMpower 010 study, the FDA has approved atezolizumab as adjuvant treatment for patients with the tumor PD-L1 expression ≥ 1% stage II to IIIA NSCLC after resection and platinum-based adjuvant chemotherapy. However, in IMpower010 clinical trial, the stratification of PD-L1 expression showed that the benefit of PD-L1 positive patients mainly came from patients with PD-L1 expression ≥50%. In all patients in the stage II - IIIA patients with PD-L1 expression ≥50%, the Hazard ratio (95%CI) of DFS was 0.43 (0.27 - 0.68). While in the PD-L1 expression 1% - 49% group, HR (95% CI) was 0·87 (0·60 - 1·26), and some patients did not benefit from adjuvant immunotherapy. This study did not exclude *EGFR/ALK* positive patients. However, EGFR/ALK positive patients do not benefit from adjuvant immunotherapy.

Postoperative adjuvant therapy will become more and more accurate. Postoperative adjuvant therapy with EGFR TKI should be considered for patients with *EGFR*-positive NSCLC. However, not all patients have achieved good clinical outcomes with EGFR TKI, increasing the need for further biomarker assessment. Studies have shown the interplay between predictive genomic signatures and clinical outcomes, and have identified that predictive markers could potentially stratify resected NSCLC patients with *EGFR* positive, which provided the precise guidance for future personalized adjuvant therapy [10]. In patients with *EGFR* combined with multiple driver gene mutations, combination or sequential adjuvant therapy may be considered [11]. In IMpower010, although patients with *EGFR/ALK* positive entirety did not benefit, HR (95% CI) was 0.99 (0.60 – 1.62) in the *EGFR* mutation group and 1.04 (0.38 – 2.90) in the *ALK* mutation group and the value was large span. Patients with *EGFR/ALK* positive and simultaneously high PD-L1 expression may also benefit from adjuvant immunotherapy.

There are still many issues and directions to be explored in the selection of postoperative adjuvant therapy. Firstly, which postoperative adjuvant therapy is better for patients with *EGFR/ALK* positive and PD-L1 expression ≥50% needs to be explorred. Secondly, how to accurately screen the benefit population of adjuvant immunotherapy for patients with *EGFR/ALK* negative and PD-L1 expression < 50%. Thirdly, treatment options for patients with recurrence and metastasis can also be explored in the future.

Specific biomarker differences may affect the efficacy of postoperative adjuvant, and subsequent analysis of specific patients requires relevant clinical trials. CtDNA-based molecular residual disease (MRD) has been explored for postoperative adjuvant chemotherapy. Both postoperative and post-adjuvant-ACT ctDNA positivity were associated with worse recurrence-free survival (RFS) significantly. In stage II-III resected NSCLC patients, the postoperative ctDNA positive group can benefit from adjuvant ACT, while ctDNA negative patients cannot [12]. MRD can also be combined to design more refined comparison of biomarker for more precise treatment in postoperative targeted and immune-therapy in the future. For example, in postoperative ctDNA positive patients with *EGFR* positive, adjuvant targeted therapy can be considered and in postoperative ctDNA positive patients with *EGFR* negative,

postoperative ACT sequential adjuvant immunotherapy can be considered. Patients with ctDNA positive after ACT can choose sequential immune-therapy or targeted therapy according to the mutate type of the driver gene.

In conclusion, both postoperative adjuvant targeted therapy and immunotherapy have the benefits of DFS, but it remains to be observed whether the benefits of DFS can be transformed into the benefits of OS. Finer patient stratification and adjuvant treatment options need to be further explored.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from the patient for participating in this case.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no Competing interests.

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Authors' contributions

Qiuyu Hou and Ningning Luo collected data and wrote the first draft of the manuscript. Xinglong Fan supervised the work. All authors critically reviewed the manuscript.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflicts of interest.

Research involving Human Participants and/or Animals

No, this research did not involve human participants.

Informed consent

Not applicable.

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